A Case Report of a Dual Diagnosis Patient: Naltrexone for the Treatment of Severe Nitrous Oxide Use Disorder with Associated Neurological and Psychiatric Sequelae

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EDITORIAL

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ABSTRACT

Background: Nitrous oxide (N_2O) is a non-regulated substance with increasing prevalence as a drug of abuse. N_2O abuse is associated with both neurological and psychiatric sequelae, including psychotic symptoms. Patients who experience substance-induced psychosis maintain a significantly elevated risk for the development of a primary mood or psychotic disorder with continued substance abuse. There is minimal research into N_2O abuse, and no FDA-approved treatment.

Methods: This report presents a patient whose severe inhalant use disorder with significant neurological and psychiatric complications was treated with naltrexone.

Results: After the initiation of oral naltrexone, the patient's use decreased by more than half, from 1500 to 500–750 cartridges daily. The addition of long-acting naltrexone was associated with a continued decrease in cravings.

Significance: This case is the first report of using naltrexone for inhalant use disorder in a patient with neurological and psychiatric complications. By using naltrexone to decrease the risk of relapse, the risk for conversion to a primary mood or psychotic disorder may decrease.

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BACKGROUND

Nitrous oxide (N_2O) is a gaseous chemical compound with analgesic, anxiolytic, and euphoric properties when ingested. N_2O is the most widely used general anesthetic agent, often combined with other agents [1]. In the United States, N_2O is a non-regulated substance and is available at auto, hardware, and food supply stores. Previously thought to have little abuse potential [2], N_2O abuse has become increasingly recognized over the past two decades [3]. In 2019, the National Survey on Drug Use and Health found 4.6% lifetime recreational use among individuals twelve and older, with prevalence increasing with age [4].

Three putative mechanisms explain the effects of N_2O. The analgesic properties of the drug are thought to be due to the release of endogenous opioids in the periaqueductal grey of the midbrain, leading to descending activation of noradrenergic neurons which decreases nociception. Additionally, N_2O functions as an agonist for the GABAa subunit, leading to anxiolytic effects similar to benzodiazepines. Lastly, NMDA receptor antagonism, similar to ketamine, is thought to mediate euphoric effects of nitrous oxide use [1].

Serious medical and psychiatric complications caused by excessive nitrous oxide use have been reported [5]. These effects are thought to be at least partially mediated by altered vitamin B12 metabolism; N_2O irreversibly binds the cobalt atom of vitamin B12, leading to loss of function of methionine synthase and accumulation of homocysteine [5]. Direct neurotoxicity of N_2O itself has also been demonstrated [6]. In 2016, a systematic review of 91 cases of complications of nitrous oxide use found neurologic complications were common (n = 72), with myeloneuropathy and subacute combined degeneration noted [6]. Several case studies reported neuropsychiatric effects (n = 11), particularly psychosis, including paranoid delusions. Medical complications of ingestion of N_2O include pulmonary toxicity and frostbite; death most frequently occurs due to hypoxic asphyxiation while using N_2O [3].

Regarding treatment and prognosis, as of 2022, no medical treatment is FDA-approved for N_2O abuse. Case reports support the use of high dose B12 to treat neurological symptoms [3, 7]. Antipsychotics have also been used successfully to treat psychiatric complications, alone or in combination with B12 supplementation. While the prognosis for acute neuropsychiatric symptoms is favorable, one study suggests that patients with substance-induced psychosis retain a 32% risk of future conversion to a primary mood and psychotic disorder [8].

Research surrounding N_2O abuse and treatment is limited in spite of the significantly elevated risk for development of future primary psychiatric disorders. In 2020, Ickowicz, Brar, and Nolan described the use of oral naltrexone to treat a 41-year-old man with N_2O use disorder without the presence of neuropsychiatric symptoms. They reported a decrease in N_2O use from about 400 eight-gram cartridges a day to fewer than 60 cartridges per week [9]. We add to this literature by describing the use of both oral and long-acting naltrexone in a patient with significant neurological and psychiatric symptoms from severe N_2O abuse.

CASE PRESENTATION

We obtained written consent for this case report. A 30-year-old male veteran self-presented to a Veteran's Affairs Hospital emergency room for bizarre and paranoid delusions in the context of significant N_2O abuse. Though recently diagnosed with B12 deficiency associated with N_2O use disorder, the patient had not yet received treatment. Past psychiatric history was significant for one previous hospitalization for substance-induced psychosis, major depressive disorder, and generalized anxiety disorder.

Substance use history was significant for many previous substances, though currently and most notably, N_2O inhalation. The patient reported first use of N_2O as a teenager, and then again as a 28-year-old in the context of psychosocial stressors. Within the span of a few months, his use escalated from forty-eight 8g canisters daily to an estimated five hundred canisters daily. During this period, he began noticing "jolt-like" sensations down his spine and legs, along with decreased concentration. Shortly thereafter, the patient was fired from his job due to his substance use. He attended a 21-day inpatient rehab program, however he felt belittled by peers who did not consider N_2O a true drug of abuse.

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The patient subsequently maintained several months of sobriety from N_2O before relapsing. His use quickly escalated to 1500 canisters daily, with 50 minutes of every waking hour spent obtaining or using N_2O. He began experiencing religious delusions, along with auditory and visual hallucinations. During his first hospitalization for substance-induced psychosis, the patient was stabilized on intramuscular Risperdal for psychosis and oral naltrexone for cravings. After this initial hospitalization, the patient reported that his N_2O use reduced by more than half from 1500 to 500 canisters per day, along with a subjective experience of decreased cravings. After several months of reduced substance use, in the context of worsening psychosocial stressors including being unhoused, the patient did not adhere to his prescribed Risperdal and naltrexone, and subsequently relapsed. His N_2O use quickly escalated with a concomitant return of psychotic symptoms.

At the time of his second psychiatric admission, his vital signs were stable. His mental status exam was notable for bizarre and paranoid delusions, in addition to the report of visual hallucinations. His neurological exam was significant for numbness and tingling in extremities, decreased concentration, back pain radiating down the spinal column, and diminished balance. Serum B12 and methyl malonic acid were within normal limits, with elevated homocysteine (14.5, reference range 3.7–13.9).

Recognizing this patient as managing both a substance use disorder and significant psychiatric symptomatology, a multi-faceted treatment approach was required. For treatment of his substance-induced psychosis, aripiprazole was initiated, resulting in a marked decrease in paranoid delusions, religious preoccupation, and visual hallucinations. Given the strong clinical effect, the patient was subsequently transitioned to intramuscular, long-acting aripiprazole for continued prevention of psychotic symptoms. Concerning his N_2O abuse, the patient requested continuation of naltrexone citing its "decrease of my intense anxiety." He further explained that with naltrexone, "I still want to use, but I no longer *need* to use." The patient was subsequently transitioned to Vivitrol (naltrexone) 380 mg intramuscular with a reported continued decrease in cravings and anxiety. For his neurological sequelae, the patient completed a five-day course of B12 1000 mcg IM, followed by a three-month prescription for oral supplementation. He reported a substantial decrease in spinal pain and paresthesia, along with improvement of balance and concentration.

DISCUSSION

We have presented the case of a patient dually diagnosed with severe inhalant use disorder associated with neurological and psychiatric sequelae. The patient was treated with both oral and intramuscular naltrexone resulting in an objective and substantial decrease in substance use, along with a reported diminishment of cravings and anxiety. Moreover, the addition of an atypical antipsychotic led to remission of his psychotic symptoms. The further utilization of the long-acting injectable form of the antipsychotic allowed for sustained protection against the reemergence of psychotic symptoms. Through management of both his inhalant use disorder and substance-induced psychosis, the patient was able to recognize the severity of his addiction and enroll in further treatment.

This case is notable for several reasons. To our knowledge, this is the first case reporting on the use of naltrexone in a patient with the combination of severe neurological and psychiatric consequences originating from N_2O use disorder. The only other case discussing the use of naltrexone for N_2O abuse was in a patient who did not experience either neurological or psychiatric sequelae. Consequently, this case demonstrates that in the presence of neuropsychiatric symptoms, the utilization of naltrexone in management of N_2O abuse may still provide clinical benefit in terms of reduced N_2O use, cravings and anxiety.

Additionally, this case is the first to report using long-acting naltrexone for N_2O inhalant use disorder. Given that momentary lapses and impulsivity play a substantial role in relapse, the monthly injectable form as opposed to a daily oral medication represents a unique opportunity to reduce substance use. The sustained reduction of abuse is particularly important for patients who present with substance-induced psychotic symptoms, given the significantly elevated risk of conversion to a primary psychiatric illness [8]. The risk of conversion increases with continued abuse; thus the long-acting form of a medication to protect against relapses may play an especially important role in the treatment of patients with dual diagnoses.

This case is also notable for the significant psychiatric sequelae resulting from the N_2O abuse. An increasing number of case reports have described psychiatric symptoms, most commonly delusions, cognitive impairment, and visual hallucinations as the primary reason for seeking treatment from N_2O use. Consequently, it is important for clinicians to consider the possibility of N_2O use in new onset psychosis. In recognizing that patients presenting with substance-induced psychosis are at elevated risk for future development of a primary psychiatric illness, this case demonstrates the importance of antipsychotic medications in the treatment regimen.

Lastly, this case also raises a point of discussion regarding the perception of one's addiction based on the substance being abused. The patient reported several episodes where he was told by peers, and subsequently began to believe, that his addiction was less severe because his primary drug of abuse was N_2O. The American Society of Addiction Medicine describes addiction as the continued and compulsive use of substances despite harmful consequences [10]. The patient discussed in this case experienced possibly lifelong psychiatric and neurological ramifications from his substance use disorder. Moreover, his use resulted in the loss of his job, housing and several close personal relationships. Discussing these consequences helped the patient internalize that though his use did not revolve around the more commonly abused substances of alcohol, opiates, or stimulants, his addiction was significant and deserving of treatment. As such, this case serves as an example that serious addiction may stem from any drug of abuse.

In summary, this case is the first to report on using both oral and long-acting naltrexone for the treatment of N_2O use disorder in a patient with significant neurological and psychiatric sequelae. Given the adverse effects associated with N_2O abuse, in addition to the significantly increased risk for development of a primary psychiatric illness with continued substance abuse, further research should explore possible treatment modalities more widely.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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REFERENCES

1. **Emmanouil D, Papadopoulou-Daifoti Z, Hagihara P, Quock D, Quock R.** A study of the role of serotonin in the anxiolytic effect of nitrous oxide in rodents. *Pharmacol Biochem Behav*. 2006; 84(2): 313–320. DOI: https://doi.org/10.1016/j.pbb.2006.05.016
2. **Gillman M.** Nitrous oxide has a very low abuse potential. *Addiction*. 1995; 90(3): 439. DOI: https://doi.org/10.1111/j.1360-0443.1995.tb03791.x
3. **Garakani A, Jaffe R, Savla D,** et al. Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: a systematic review of the case literature. *American J Addiction*. 2016; 25(5): 358–369. DOI: https://doi.org/10.1111/ajad.12372
4. **National Survey on Drug Use and Health.** *Table 1.97B - Specific Hallucinogen, Inhalant, Needle, Heroin, and Other Drug Use in Lifetime among Persons Aged 12 or Older, by Age Group: Percentages, 2018 and 2019*. SAMHSA, Center for Behavioral Health Statistics and Quality; 2014.

5. **Savage S, Ma D.** The neurotoxicity of nitrous oxide: the facts and "putative" mechanisms. *Brain Sci*. 2014; 4(1): 73–90. DOI: https://doi.org/10.3390/brainsci4010073
6. **Jevtovic-Todorovic V, Beals J, Benshoff N, Olney J.** Prolonged exposure to inhalational anesthetic nitrous oxide kills neurons in adult rat brain. *Neuroscience*. 2003; 122(3): 609–616. DOI: https://doi.org/10.1016/j.neuroscience.2003.07.012
7. **Chen T, Zhong N, Jiang H, Zhao M, Chen Z, Sun H.** Neuropsychiatric symptoms induced by large doses of nitrous oxide inhalation: a case report. *Shanghai Arch Psychiatry*. 2018; 30(1): 56. DOI: https://doi.org/ 10.11919/j.issn.1002-0829.217084
8. **Starzer M, Nordentoft M, Hjorthog C.** Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis. *Am J Psychiatry*. 2018; 175(4): 343–350. DOI: https://doi.org/10.1176/appi.ajp.2017.17020223
9. **Ickowicz S, Brar R, Nolan S.** Case Study: Naltrexone for the Treatment of Nitrous Oxide Use. *J Addiction Med*. 2020; 14(5): e277–e279. DOI: https://doi.org/10.1097/ADM.0000000000000642
10. **American Society of Addiction Medicine.** What is the definition of addiction? Updated September 15, 2019. https://www.asam.org/quality-care/definition-of-addiction.

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